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EXAMINER	
PARAS JR,P	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No. 09/344,189	Applicant(s) ROGLER, CHARLES E.	
	Examiner Peter Paras	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .

18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other: .

Applicants' amendment received on March 12, 2001 (Paper No. 10) has been entered. Claims 1 and 8 have been amended. Claims 1-36 are pending and are currently under consideration.

Inventorship

In view of the papers filed on March 12, 2001, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by the addition of Jeorg Petersen.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Oath/Declaration

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

The following are new grounds of rejection under 35 U.S.C. 112, first paragraph:

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a chimeric, immunodeficient (SCID) mouse, lacking mature B and T cells and having a degenerated liver parenchyma which is repopulated with transplanted mammalian hepatocytes that are infected with a compatible hepatitis virus, wherein the mouse is homozygous for a transgene encoding a urokinase-type plasminogen activator (uPA), which causes the liver degeneration; and methods of using the same mouse does not reasonably provide enablement for a method of making any chimeric, immunetolerant mouse having a degenerated liver and comprising xenogenic mammalian hepatocytes which can be infected with a compatible hepatitis virus; and methods of using the same chimeric, immunetolerant mouse. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification discusses that the invention features a chimeric mouse liver system for mammalian hepatitis. See page 7, lines 30-35. The specification discusses that the invention features a chimeric, immunetolerant mouse, with a degenerated liver comprising mammalian xenogenic hepatocytes, which can be infected with a compatible hepatitis virus. The specification goes on to discuss the creation of a chimeric, immunodeficient (SCID) mouse comprising disrupted RAG-2 genes [which causes immunodeficiency such that the mouse lacks mature B and T cells], and a uPA transgene [which causes liver degeneration]. See page 5. While the specification

provides extensive teachings pertaining to the creation of a uPA/SCID homozygous mouse [which is created by breeding a uPA transgenic mouse with a RAG-2 knockout mouse] which has a degenerated liver and lacks mature B and T cells such that the uPA/SCID mouse is a recipient for transplanted mammalian hepatocytes that are infected with a compatible hepatitis virus, the specification fails to provide any relevant teachings or specific guidance with regard to the generation of any immunetolerant, chimeric mouse having a degenerated liver and comprising mammalian hepatocytes. Thus, as enablement requires the specification to teach how to make and use the claimed invention without undue experimentation, the specification fails to enable the production of any immunetolerant mouse having a degenerated liver which can be transplanted with xenogenic mammalian hepatocytes and infected with a compatible hepatitis virus such that the mouse may be used as a liver model system for mammalian hepatitis.

As a first issue, the art of transplantation is unpredictable with respect to transplant success when using immunotolerant mice as recipients of xenogenic transplants. With regard to claim breadth, immunetolerant mice can encompass any mouse with even a slightly suppressed immune system, such as a mouse with a cold. However, it is unpredictable if an immunetolerant mouse, other than a SCID mouse, can stably tolerate liver transplants. The state of the art suggests that SCID mice are superior acceptors of xenogenic tissue transplants, particularly liver transplants, as SCID mice are devoid of functional B and T cells. See Baumgardner et al (2000, Immunological Reviews, 174: 260-279), abstract. Baumgardner observes that some

immunetolerant mice such as CD4 knockouts, CD8 knockouts, B-cell knockouts, MHCII knockouts, CD4+ reconstituted SCID mice, and CD8+ reconstituted SCID mice all reject transplanted liver tissue. See page 268, Table 2, and throughout the whole document. In view of the unpredictability of the tolerance of xenogenic liver transplants into immunotolerant mouse, it would have required undue experimentation to attempt to transplant xenogenic liver cells in any immunetolerant mouse.

Furthermore, it is unpredictable if transplanted xenogenic hepatocytes in any immunetolerant mouse can be infected *in vivo* with a compatible hepatitis virus, after transplantation. Humoral and cellular elements of the host immune system are known to be important for clearance of hepatitis B virus. The humoral response to HBV antigens helps clear circulating virions and confers protection against reinfection, whereas T cell-mediated responses eliminate infected cells. See Petersen et al (PNAS, 1998, 95: 310-315), page 310. In view of the host humoral and cellular immune response that may be present in any of the broadly claimed immunetolerant mice it is unpredictable if hepatitis virus introduced into such a mouse can infect transplanted hepatocytes or if transplanted hepatitis infected mammalian hepatocytes can survive the host's immune response to create a model for mammalian hepatitis. The specification only provides working examples directed to transplantation of woodchuck hepatocytes, into the parenchyma of a degenerated liver in a uPA/ SCID (RAG-2) homozygous mouse, wherein the transplanted hepatocytes are either preinfected or infected after transplantation with woodchuck hepatitis virus. Given the differences in immune systems of the broadly encompassed immunetolerant mice it would be

unpredictable to infect transplanted liver cells in such immunetolerant mice with a compatible hepatitis virus.

Finally, with regard to liver degeneration, it is unpredictable if any chimeric, immunetolerant mouse having a liver degenerated by any method can stably support transplanted xenogenic mammalian hepatocytes. The instant specification describes a transgenic mouse comprising a uPA transgene, wherein expression of uPA results in liver degeneration. The specification, however, does not support liver degeneration by any other method. It would be unpredictable if liver degeneration by other methods would allow transplantation and reconstitution of the host liver by xenogenic hepatocytes. Other methods of liver degeneration, such as administration of liver toxic chemicals, would kill both host hepatocytes and donated hepatocytes and would allow competition for reconstitution of the liver between host and transplanted hepatocytes. Furthermore, the state of the art suggests that only a homozygous uPA transgenic mouse can stably support transplanted xenogenic mammalian hepatocytes. This observation is supported by Rhim et al (PNAS, 1995, 92: 4942-4946) who report that in hemizygous mice transgene inactivation is a relatively frequent event, often resulting in hundreds of clonal nodules of host-derived cells that no longer express the transgene. The clonal cell nodules have a growth advantage relative to uPA expressing hepatocytes and can completely replace the transgenic liver while competing with transplanted hepatocytes. Transgene inactivation is a less common event in homozygous uPA transgenic mice, consistent with the fact that two transgene arrays must be inactivated, allowing the transgenic liver to persist longer facilitating the

complete replacement of the liver by donated hepatocytes as there is a lack of competition from hepatocyte nodules that do not express the uPA transgene. See page 4942. Given, the differences between the immune systems of immunetolerant mice and transgene inactivation in hemizygous uPA transgenic mice it would have required undue experimentation to transplant xenogenic hepatocytes into the liver of a uPA hemizygous mouse that is immunetolerant.

Additionally, with respect to infection of xenogenic hepatocytes with species-specific hepatitis virus, it is unpredictable if any hepatitis virus can infect hepatocytes of any mammalian species. See Fields Virology, 1996, page 990. For example hepadnaviruses (which include human hepatitis B virus, woodchuck hepatitis virus, ground squirrel hepatitis virus, and duck B hepatitis virus) have a moderately narrow host range, in particular human hepatitis B virus can infect only humans in nature and under experimental conditions chimpanzees. Of the other hepatitis viruses recited in the claims the host range of infectivity is limited, for example hepatitis C virus and infect humans and non-human primates, and hepatitis E and F viruses can only infect humans. As such as the host range of infectivity of hepatitis viruses is limited it is unpredictable if all the hepatitis viruses recited in the claims can infect any xenogenic hepatocyte recited in the claims.

Furthermore, with respect to claims 15, 17-20, and 22 it is unpredictable if any mammalian virus can infect a hepatocyte as recited in the claim. The state of the art is such that hepatitis viruses infect hepatocytes in a limited species-specific manner. See

above. The specification does not support with teachings or guidance infection of hepatocytes with mammalian viruses other than hepatitis viruses.

Lastly, with regard to claims 25-36, it is unpredictable if all hepatitis viruses will transform hepatocytes resulting in hepatocellular carcinoma (HCC). While state of the art supports that chronic human hepatitis B and C infection and woodchuck hepatitis virus infection can result in HCC (see Fields virology, 1996), it is unpredictable and not supported by the art that infection by other hepatitis viruses like hepatitis F virus, hepatitis E virus, hepatitis D virus, ground squirrel hepatitis virus, and hepatitis A virus can result in HCC.

Therefore, in view of the lack of direction or guidance provided by the specification which teaches the production of any immunetolerant, chimeric mouse having a degenerated liver; the unpredictability of transplanting xenogenic hepatocytes into any immunetolerant mouse; the unpredictability of transplanting xenogenic hepatocytes into an immunetolerant, hemizygous uPA transgenic mouse; the unpredictability of infecting any mammalian hepatocyte with any mammalian virus; the breadth of the claims drawn to any mammalian virus and any mammalian hepatocyte; the breadth of the claims drawn to any immunetolerant mice, and the breadth of the claims drawn to any method of liver degeneration, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Applicant's arguments have been fully considered but they are not persuasive. Applicants have argued the instant specification has disclosed immunetolerant mice deficient in B and T cells, such as Rag-1 knockout mice, Rag-2 knockout mice, nude

mice, and SCID mice. Applicants also have submitted Janeway et al as support for immunetolerant mice. Specifically, Applicants point out that Janeway teaches that mice with mutations in any of RAG-1, Rag-2 or scid genes are deficient in B and T cells are immunetolerant mice. See the Amendment on pages 3-4.

In response, the Examiner asserts that the term "immunetolerant mouse" encompasses a much broader scope than a mouse lacking B and T cells. The term immunetolerant mouse can encompass any mouse with even a slightly suppressed immune system, such as a mouse with a cold. Applicants have even acknowledged the breadth of the term "immunetolerant mouse" by first citing that the instant specification recites Rag-1 KO, Rag-2 KO, nude, and scid mice as immunetolerant and then providing the Janeway reference for support, which recites only RAG-1 KO, Rag-2 KO, or scid mice as immunetolerant. See the amendment on page 4, lines 5-8. Applicants have created a dichotomy regarding the term immunetolerant by suggesting that both nude mice and mice with scid phenotypes (scid, Rag-1 KO, Rag-2 KO) are immunetolerant mice that lack B and T cells. See page 3, 2nd paragraph from the top, of the amendment. Clearly, nude mice (which lack T cells) and mice with scid phenotypes (which lack B and T cells) are different with regard to tolerance of implanted xenogenic hepatocytes. The state of the art suggests that mice with scid phenotypes are superior acceptors of xenogenic tissue transplants, particularly liver transplants, as SCID mice are devoid of functional B and T cells. See Baumgardner et al above. Furthermore, humoral and cellular elements of the host immune system are known to be important for clearance of hepatitis B virus. The humoral response to HBV antigens helps clear

circulating virions and confers protection against reinfection, whereas T cell-mediated responses eliminate infected cells. See Petersen above. In view of the host humoral and cellular immune response that may be present in any of the broadly claimed immunetolerant mice it is unpredictable if hepatitis virus introduced into such a mouse can infect transplanted hepatocytes or if transplanted hepatitis infected mammalian hepatocytes can survive the host's immune response to create a model for mammalian hepatitis.

Applicants argue that a degenerated liver is a diseased liver having biochemical function, which leads to either hepatocyte death and/or inability to replicate. Applicants allege that it would have been routine for one of ordinary skill in the art to obtain degenerated liver using any established protocol and that it would have been further routine to repopulate such degenerated livers with xenogenic hepatocytes. See the amendment on page 5.

In response, the Examiner asserts that while it may be possible to create a degenerated liver by administration of chemicals or other means, only mice that are immunodeficient, devoid of B and T cells, and which are homozygous transgenic for the uPA transgene operably linked to the albumin promoter can successfully tolerate implantation of xenogenic hepatocytes. It would be unpredictable if liver degeneration by other methods would allow transplantation and reconstitution of the host liver by xenogenic hepatocytes. Other methods of liver degeneration, such as administration of liver toxic chemicals, would kill both host hepatocytes and donated hepatocytes and would allow competition for reconstitution of the liver between host and transplanted

hepatocytes. Furthermore, the state of the art suggests that only a homozygous uPA transgenic mouse can stably support transplanted xenogenic mammalian hepatocytes. This observation is supported by Rhim et al, see above, who suggests that in hemizygous mice transgene inactivation is a relatively frequent event, often resulting in hundreds of clonal nodules of host-derived cells that no longer express the transgene. The clonal cell nodules have a growth advantage relative to uPA expressing hepatocytes and can completely replace the transgenic liver while competing with transplanted hepatocytes. Transgene inactivation is a less common event in homozygous uPA transgenic mice, consistent with the fact that two transgene arrays must be inactivated, allowing the transgenic liver to persist longer facilitating the complete replacement of the liver by donated hepatocytes as there is a lack of competition from hepatocyte nodules that do not express the uPA transgene.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The previous rejection of claims 1-14 is under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is obviated in view of Applicants amendments to the claims, removing the phrase "capable of".

The following are new grounds of rejection under 35 U.S.C. 112, second paragraph:

Claims 1-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 is indefinite as written. The language "derived" implies manipulation to a hepatocyte that has been isolated from a woodchuck. As such it is unclear how exactly the hepatocyte has been manipulated other than to be isolated from a woodchuck liver. The specification has taught isolation of hepatocytes from a woodchuck but has not taught any other manipulation of woodchuck hepatocyte prior to implanting. Correction is required.

Claims 1, 5, 7, 8, 12, 15, 19, 21, 25, 33, and 35 recite language that is indefinite. The term "compatible" does not have a clear meaning with regard to a hepatitis virus infecting a hepatocyte. Also it is unclear from the specification what other mammalian viruses are "compatible" with liver infection as the specification only discusses infection of hepatocytes with species-specific hepatitis viruses. It is clear that the infectivity of hepatitis viruses is species specific, for example a woodchuck hepatitis virus will infect woodchuck hepatocytes but not human hepatocytes, while a hepatitis E virus will infect human and non-human primate hepatocytes but not woodchuck hepatocytes. Clarification of the claim language is necessary to reflect the species specificity of hepatitis viruses with regard to infectivity of mammalian hepatocytes. Claims 2-4, 6, 9-11, 13-14, 16-18, 20, 22-24, 26-32, 34, and 36 depend from claims 1, 8, 15, and 25.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless-
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The prior rejection of claims 1-36 under 35 U.S.C. 102(a) as being anticipated by Petersen et al (PNAS, 1998, 95: 310-315) is obviated in view of Applicants' Declaration under 37 C.F.R. 1.132.

The following are new grounds of rejection under 35 U.S.C. 102(e):

Claims 1-5, 8-12, 15-21, 24, 25-33, and 36 are rejected under 35 U.S.C. 102(e) as being anticipated by Kay et al.

The claims are directed to a chimeric, immunodeficient (SCID) mouse model with a degenerated liver, wherein xenogenic mammalian hepatocytes, are transplanted into the liver parenchyma of the mouse and infected with the appropriate species-specific hepatitis virus. The claims are also directed to methods of making the same mouse. The claims are further directed methods of using the same mouse for screening potential antiviral and anticancer compounds.

Kay et al teach a chimeric SCID mouse expressing in its liver a uPA transgene the expression of which causes liver degeneration and comprising human hepatocytes. See columns 7-8. Kay et al teach that such a mouse can be used as a model of hepatitis infection, particularly hepatitis A, B, and C. Kay et al also teach that ribozymes, hormones, cytokines, enzymes, antigens, antibodies, clotting factors, anti-sense RNA, regulatory proteins, fusion proteins and the like, may be used for treating a disease [particularly hepatitis, hepatocellular carcinoma that results from chronic hepatitis B or C infection] in the same chimeric mouse model. Particularly Kay et al teach that ribozymes may be used to inhibit HCV replication, which can be assayed by quantitative RT-PCR.

Thus, the teachings of Kay et al anticipate all of the instant claim limitations.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The previous rejection of claims 1-36 under 35 U.S.C. 103(a) as being unpatentable over Rhim et al in view of Roggendorf is withdrawn in view of lack of motivation to combine the cited references as argued by Applicants in Paper No. 10.

The following are new grounds of rejection under 35 U.S.C. 103(a):

Claims 1-5, 8-9, and 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhim et al (PNAS, 1995, 92: 4942-4946) taken with Vierling (US 6,034,297).

The claims are directed to a chimeric, immunodeficient (SCID) mouse model that is homozygous for a uPA transgene rendering the immunodeficient mouse with a degenerated liver, wherein xenogenic mammalian hepatocytes are transplanted into the liver parenchyma of the mouse and infected with the appropriate species-specific hepatitis virus. The claims are also directed to methods of making the same mouse comprising breeding a homozygous uPA transgenic mouse and a homozygous SCID mouse.

Rhim et al teach a chimeric nude mouse comprising a homozygous uPA transgene and rat hepatocytes that have been transplanted into the liver parenchyma of the same mouse; the mouse is created by breeding a homozygous uPA mouse with a homozygous nude mouse. Rhim et al teach that expression of the uPA transgene results in liver degeneration in transgenic mice; homozygous uPA transgenic mice would be ideal for assessing liver cell growth as the lack of competition from non-transgenic host liver cells allows the donated liver cells to completely replace the recipient liver. In particular, Rhim et al suggest that xenogenic hepatocytes from other species could reconstitute the liver of such a mouse. See page 4942. Rhim et al discuss that such a mouse would be useful for studying liver biology of other species, including humans, particularly for carcinogenicity studies or as models for liver disease.

See pages 4942 and 4946. Rhim et al differ from the claimed invention by not teaching infection of transplanted hepatocytes in a chimeric uPA transgenic mouse with a hepatitis virus.

However at the time the claimed invention was made, chimeric immunodeficient (SCID) mice comprising xenogenic tissue, particularly xenogenic hepatocytes were well within the routine skill of the ordinary artisan. In particular, Vierling et al teach a chimeric homozygous severe combined immunodeficiency (SCID) mouse comprising human hepatocytes infected [prior to transplantation] with hepatitis C virus that have been transplanted into the liver parenchyma. See the example in columns 3-4. Vierling et al specifically discuss that SCID mice are used as recipients of donor hepatocytes because the donor hepatocytes are not rejected due to the severe immunodeficiency of the SCID mouse. See column 4. Vierling et al suggest a definite need for an animal model comprising HCV infected xenogenic hepatocytes that remain viable and morphologically intact in donor tissue and replicate HCV, for studying the biology and therapy of HCV. See column 1.

Accordingly, in view of the routine state of the art as presented by Vierling et al it would have been obvious to modify the chimeric mouse of Rhim et al by breeding a homozygous SCID mouse with a homozygous uPA transgenic mouse to create a homozygous uPA SCID mouse that is immunodeficient and has a degenerated liver such that xenogenic mammalian hepatocytes may be transplanted into the liver parenchyma, wherein the xenogenic hepatocytes are infected with the appropriate species-specific hepatitis virus with a reasonable expectation of success. One of

ordinary skill would have been sufficiently motivated to make such a modification as it was an art-recognized goal to create an animal model for hepatitis infection as taught by Vierling et al. In particular, one of ordinary skill would have been motivated to breed a homozygous uPA transgenic mouse with a SCID mouse to create a homozygous uPA/SCID mouse because Vierling has taught that a SCID mouse does not reject xenogenic liver tissue and Rhim has taught that the liver of a homozygous uPA transgenic mouse can be completely reconstituted with xenogenic hepatocytes making such a mouse valuable for studying liver disease, including cancer.

Thus, the claimed invention, as a whole, was clearly prima facie obvious in the absence of evidence to the contrary.

Claims 6, 10, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhim taken with Vierling as applied to claims 1-5, 8-9, and 11-12 above and further in view of Alt et al (US 5,583,278).

The claims are directed to a homozygous uPA/RAG-2 knockout transgenic mouse and a method of breeding a uPA transgenic mouse with a RAG-2 knockout homozygous transgenic mouse to create a uPA/RAG-2 knockout homozygous mouse.

Rhim et al teach a chimeric nude mouse comprising a homozygous uPA transgene and rat hepatocytes that have been transplanted into the liver parenchyma of the same mouse; the mouse is created by breeding a homozygous uPA mouse with a homozygous nude mouse. Rhim et al teach that expression of the uPA transgene results in liver degeneration in transgenic mice; homozygous uPA transgenic mice

would be ideal for assessing liver cell growth as the lack of competition from non-transgenic host liver cells allows the donated liver cells to completely replace the recipient liver. In particular, Rhim et al suggest that xenogenic hepatocytes from other species could reconstitute the liver of such a mouse. See page 4942. Rhim et al discuss that such a mouse would be useful for studying liver biology of other species, including humans, particularly for carcinogenicity studies or as models for liver disease. See pages 4942 and 4946. Rhim et al differ from the claimed invention by not teaching infection of transplanted hepatocytes in a chimeric uPA transgenic mouse with a hepatitis virus.

However at the time the claimed invention was made, chimeric immunodeficient (SCID) mice comprising xenogenic tissue, particularly xenogenic hepatocytes were well within the routine skill of the ordinary artisan. In particular, Vierling et al teach a chimeric homozygous severe combined immunodeficiency (SCID) mouse comprising human hepatocytes infected [prior to transplantation] with hepatitis C virus that have been transplanted into the liver parenchyma. See the example in columns 3-4. Vierling et al specifically discuss that SCID mice are used as recipients of donor hepatocytes because the donor hepatocytes are not rejected due to the severe immunodeficiency of the SCID mouse. See column 4. Vierling et al suggest a definite need for an animal model comprising HCV infected xenogenic hepatocytes that remain viable and morphologically intact in donor tissue and replicate HCV, for studying the biology and therapy of HCV. See column 1.

The collective teachings of Rhim et al and Vierling et al do not specifically teach the use of a RAG-2 (SCID) mouse. However at the time the claimed invention was made, it was well known to the ordinary artisan that RAG-2 deficient mice have an improved SCID phenotype. Alt et al teach a severe combined immunodeficient (SCID) mouse that resulted from homozygous disrupted recombination activating gene (RAG) 2. Disruption of the RAG-2 genes results in a novel SCID phenotype. See column 2. Alt et al discuss that SCID mutated mice comprising altered VDJ recombinase genes can have a leaky phenotype resulting in production of B and T lymphocytes that can result in rejection of implanted tumor cells. RAG-2 deficient mice have an improved SCID phenotype that is not leaky. Alt et al further discuss that human tissue such as tumor cells, lymphoid progenitors, fetal liver cells may be implanted in RAG-2 deficient mice to create chimeric mice (see columns 3-4) and that such a mouse provides for methods of identifying and evaluating drugs, and evaluating different therapeutic protocols against infections, viral infections, and tumors (see column 6). Alt et al specifically discuss that the viral infection may be a hepatitis virus infection and suggest that infection of hepatocytes make occur following implantation (see column 6).

Accordingly, in view of the teachings of Alt et al it would have been obvious at the time the claimed invention was made to modify the teachings of Rhim and Vierling by breeding a RAG-2 knockout mouse with a uPA homozygous transgenic mouse to create a RAG-2/uPA homozygous mouse that can be a recipient for transplanted xenogenic hepatocytes. One of ordinary skill would have been sufficiently motivated to make such a modification because a RAG-2 homozygous knockout mouse represents a novel,

improved SCID phenotype that does not result in transplant rejection because a RAG-2 homozygous knockout mouse has a phenotype that does not result in leaky production of B and T lymphocytes as taught by Alt and more particularly because Alt has suggested that RAG-2 knockout mice may be used as recipients for transplanted liver cells and as models for testing antiviral therapies, such as hepatitis virus therapy.

Claims 7 and 14-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhim taken with Vierling in view of Alt as applied to claims 1-6 and 8-13 above and further in view of Roggendorf et al (Intervirology, 1995, 38: 100-112).

The claims are directed to a uPA/RAG-2 knockout homozygous transgenic mouse comprising woodchuck hepatocytes and are infected with woodchuck hepatitis virus and a method of creating the same mouse. The claims are further directed to methods of screening a test compound for antiviral activity comprising administering said test compound to the uPA/RAG-2 mouse comprising xenogenic mammalian hepatocytes, particularly woodchuck hepatocytes, wherein the hepatocytes are infected with the appropriate species-specific hepatitis virus and assaying the level of viral replication in response to the test compound.

Rhim et al teach a chimeric nude mouse comprising a homozygous uPA transgene and rat hepatocytes that have been transplanted into the liver parenchyma of the same mouse; the mouse is created by breeding a homozygous uPA mouse with a homozygous nude mouse. Rhim et al teach that expression of the uPA transgene results in liver degeneration in transgenic mice; homozygous uPA transgenic mice

would be ideal for assessing liver cell growth as the lack of competition from non-transgenic host liver cells allows the donated liver cells to completely replace the recipient liver. In particular, Rhim et al suggest that xenogenic hepatocytes from other species could reconstitute the liver of such a mouse. See page 4942. Rhim et al discuss that such a mouse would be useful for studying liver biology of other species, including humans, particularly for carcinogenicity studies or as models for liver disease. See pages 4942 and 4946. Rhim et al differ from the claimed invention by not teaching infection of transplanted hepatocytes in a chimeric uPA transgenic mouse with a hepatitis virus.

However at the time the claimed invention was made, chimeric immunodeficient (SCID) mice comprising xenogenic tissue, particularly xenogenic hepatocytes were well within the routine skill of the ordinary artisan. In particular, Vierling et al teach a chimeric homozygous severe combined immunodeficiency (SCID) mouse comprising human hepatocytes infected [prior to transplantation] with hepatitis C virus that have been transplanted into the liver parenchyma. See the example in columns 3-4. Vierling et al specifically discuss that SCID mice are used as recipients of donor hepatocytes because the donor hepatocytes are not rejected due to the severe immunodeficiency of the SCID mouse. See column 4. Vierling et al suggest a definite need for an animal model comprising HCV infected xenogenic hepatocytes that remain viable and morphologically intact in donor tissue and replicate HCV, for studying the biology and therapy of HCV. See column 1.

However at the time the claimed invention was made, it was well known to the ordinary artisan that RAG-2 deficient mice have an improved SCID phenotype. Alt et al teach a severe combined immunodeficient (SCID) mouse that resulted from homozygous disrupted recombination activating gene (RAG) 2. Disruption of the RAG-2 genes results in a novel SCID phenotype. See column 2. Alt et al discuss that SCID mutated mice comprising altered VDJ recombinase genes can have a leaky phenotype resulting in production of B and T lymphocytes that can result in rejection of implanted tumor cells. RAG-2 deficient mice have an improved SCID phenotype that is not leaky. Alt et al further discuss that human tissue such as tumor cells, lymphoid progenitors, fetal liver cells may be implanted in RAG-2 deficient mice to create chimeric mice (see columns 3-4) and that such a mouse provides for methods of identifying and evaluating drugs, and evaluating different therapeutic protocols against infections, viral infections, and tumors (see column 6). Alt et al specifically discuss that the viral infection may be a hepatitis virus infection and suggest that infection of hepatocytes make occur following implantation (see column 6).

The collective teachings of Rhim, Vierling, and Alt do not specifically address the use of woodchuck hepatocytes and woodchuck hepatitis virus or methods of screening compounds for antiviral activity.

However at the time the claimed invention was made, Roggendorf et al teach that the woodchuck and the woodchuck hepatitis virus (WHV) have been studied and used as the most suitable model for human hepatitis B virus infection. WHV is closed related to the human virus, having strong similarities in morphology, genome structure

and gene products, replication, epidemiology, the course of infection and in the development of illness and hepatocellular carcinoma (HCC). In particular the woodchuck is currently used as to study pathogenesis of hepadnavirus infection, molecular mechanisms of HCC development, and cell tropism of hepadnaviruses; also woodchucks are used to study different approaches for new vaccines to hepadnaviruses and evaluation of antiviral drugs in chronic WHV infection. See page 100 and abstract. Roggendorf et al discuss that chronic WHV infection almost inevitably develops into HCC. See page 104. Roggendorf et al discuss specifically in vivo testing of antiviral drugs, including immune modulators, in the woodchuck model of hepatitis, particularly chronic hepatitis infection; nucleoside analogs in particular are discussed as antiviral agents (and also as anticancer agents as treatment of chronic WHV infection would also treat HCC because chronic WHV results in HCC). See pages 108-109.

Accordingly, in view of the teachings of Roggendorf et al, at the time the claimed invention was made, it would have been obvious for one of ordinary skill in the art to modify the teachings of Rhim et al, Vierling et al, and Alt et al by creating a chimeric uPA/RAG-2 knockout homozygous mouse comprising woodchuck hepatocytes, wherein such a chimeric mouse can be used as a model for WHV infection as well as for testing potential antiviral and anticancer compounds for the prevention of WHV replication and HCC development. One of ordinary skill would have been sufficiently motivated to make such modifications as it was an art-recognized goal to create animal models of hepatitis infection that relate to human hepatitis infection for testing of antiviral and

anticancer compounds as taught by Roggendorf et al, particularly as Rhim et al has suggested use of xenogenic hepatocytes of other species for studying liver biology and liver disease.

Thus, the claimed invention as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Applicants have argued that Rhim has not suggested that a degenerated liver in an immunetolerant mouse should repopulated with xenogenic cells infected with any type of virus, much less a compatible hepatitis virus, as defined in the claims. Applicants also argue that Roggendorf et al makes no suggestion to use woodchuck hepatocytes and WHV I a transgenic animal model of any kind. Applicants further assert that the prior art at best provides only general guidance for the utility of immunetolerant Alb-uPA mice as a repository for human hepatocytes, as reagents for carcinogenicity or as models for human liver disease.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Rhim et al has suggested that Alb-uPA homozygous transgenic mice can be implanted with xenogenic

hepatocytes from different mammalian species and be used to study hepatocellular biology and human liver disease. Hepatocellular biology and liver disease certainly encompass hepatitis and hepatocellular carcinoma, which are specific types of liver disease. Vierling et al has taught the need to create a model for hepatitis and has specifically taught a SCID mouse transplanted with human hepatocytes infected with hepatitis C virus. Alt has taught the benefits of using Rag-2 knockout mice for transplantation of fetal liver cells and that such a mouse provides for methods of identifying and evaluating drugs, and evaluating different therapeutic protocols against infections, particularly viral infections, and more particularly hepatitis infection. Finally, Roggendorf has taught the woodchuck and the woodchuck hepatitis virus (WHV) have been studied and used as the most suitable model for human hepatitis B virus infection; particularly the woodchuck is currently used as to study pathogenesis of hepadnavirus infection, molecular mechanisms of HCC development, and cell tropism of hepadnaviruses. See all references above. Clearly, the cited references have provided ample motivation to create the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Peter Paras, Jr.

Art Unit 1632

JILL D. MARTIN
PRIMARY EXAMINER